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Functional germline variants in driver genes of breast cancer and APOBEC family members

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Breast cancer (BC) is in both developing and developed regions of the world the most frequent cancer among woman. In 2012 around 522,000 women died on BC and another 1.67 million new cancer cases were diagnosed worldwide. About 5-10% of women with a positive diagnose of BC do have a family history of BC, which is a known risk factor for the disease. Thus, the purpose of the thesis was to identify new genes and inherited variants which influence the development of BC.

The first hypothesis was based on the assumption, that germline variants in driver genes commonly mutated in sporadic breast tumours may contribute to BC progression. During the present thesis several SNPs in mainly four genes (*ATR*, *RUNX1*, *TBX3* and *TTN*) showed associations with BC development and progression. *TBX3* was associated with BC risk and with less aggressive tumour characteristics (rs2242442 and rs12366395). An association with BC survival and aggressive tumour characteristics were detected for the genes *ATR* (rs2227928), *RUNX1* (rs17227210) and *TTN* (rs2303838 and rs2042996). According to the experimental ENCODE data all these SNPs themselves or SNPs in high linkage disequilibrium with them ($r^2 \geq 0.8$) were located in regulatory regions and *in silico* analyses provided evidence of possible functional consequences for the associated SNPs. For *RUNX1* and specially *TTN,* strong signatures of positive selection gave further insights on the functionality of the SNPs. Altogether investigation of the described genes gave evidence that germline variants in BC driver genes may have impact on BC risk and/or survival. Future studies could discover further germline variants in known or so far unknown driver genes which contribute to cancer development

The second hypothesis was based on the influence of *APOBEC* family members to BC. These genes cause a C→T mutation signature which is associated upon others with BC development. In addition overexpression of *APOBEC3B* and the *APOBEC3A -APOBEC3B*

deletion polymorphism are associated with BC risk. Thus, SNPs with possible functional effects in the *APOBEC* members *APOBEC3A* and *APOBEC3B* were selected. SNPs rs5757402, located in APOBEC3A was associated with negative lymph node metastasis and low stage. None the genotyped SNPs showed significant association with either BC risk or survival. Investigation of the deletion polymorphism did not confirm an association with increased BC risk reported by other groups. A possible reason is the small sample size of the genotyped Swedish population together with the fact that the frequency of the deletion is about 6% in the European populations.

Although certain limitations have to be considered, the present thesis provides new knowledge about genes and mutations influencing BC risk, tumour characteristics and survival.